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Silver-Mediated Radical C(sp^3)−H Biphosphinylation and Nitration of β-Alkynyl Ketones for Accessing Functional Isochromenes

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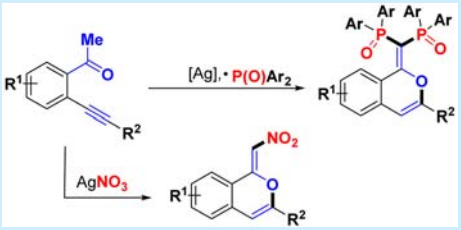
Supporting Information

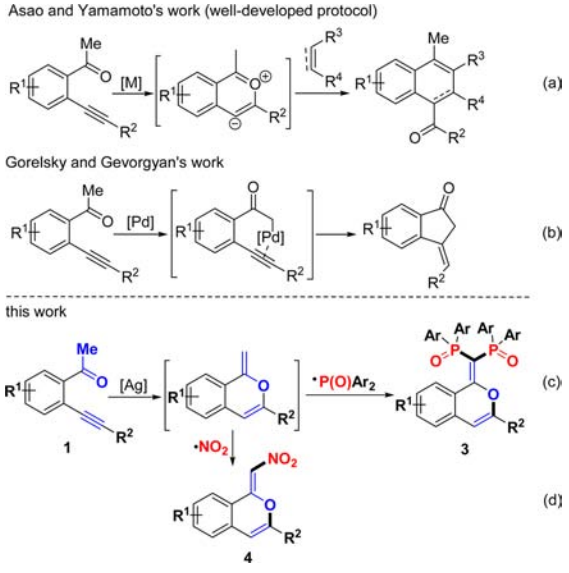
ABSTRACT: Silver-mediated C(sp^3)−H functionalization and 6-*endo-dig* oxo-cyclization of conjugated β-alkynyl ketones have been established under oxidative conditions. The reaction leads to the concise formation of a wide range of isochromenes via C(sp^3)−H bond-breaking and radical addition steps. Dual and monofunctional isochromene products were selectively controlled by using either electron-rich or electron-deficient radical sources.



Site-selective C(sp^3)−H bond functionalization has become an attractive and challenging topic in chemical science,[1] enabling the direct conversion of C(sp^3)−H bonds of common petroleum compounds to their C−C and C−heteroatom counterparts. It provides a practical and atom-economic strategy for substantially intriguing syntheses. This strategy also can avoid the use of preformed organometallic reagents for traditional cross-couplings, making the synthesis more convenient and greener.[2] Although mono C−H bond functionalization on sp^3 carbon atom has been studied well,[1,2] the dual α,α-C(sp^3)−H functionalization on the same carbon center has been much less explored so far and still remains a great challenge.[3] Recently, our group and others have independently developed radical-triggered dual C(sp^3)−H functionalization of cycloalkanes[3a] and heterocycloalkanes,[3b] resulting in double C−C bond formations on the same carbon center through C(sp^3)−H bond activation. However, to the best of our knowledge, radical-based direct conversion of dual C(sp^3)−H bonds on the same carbon atom to double C−P functionalities has not been documented yet.

It has been well established that conjugated β-alkynyl ketones **1** are competent reactants endowed with multiple reactive sites, serving as versatile precursors for many important targets of chemical and biomedical potentials.[4] In the past decade, the pioneering work of Asao and Yamamoto[5] have stimulated extensive studies on metal-catalyzed [4 + 2] cycloadditions of conjugated β-alkynyl ketones with alkenes or alkyne (Scheme 1a).[6] In the meantime, Gorelsky, Gevorgyan, and co-workers successfully established the palladium-catalyzed 5-*exo-dig* carbocyclization of conjugated β-alkynyl ketones achieving C(sp^3)−H bond functionalization of their methyl groups (Scheme 1b).[7] However, 6-*endo-dig* oxo-cyclization of β-alkynyl ketones together with its dual C(sp^3)−H bond functionalization of their methyl group has been virtually unexplored. Recently, our group has focused on the development of radical-triggered C−H functionalization reactions.[8] During this study, we planned to conduct the metal-catalyzed oxo-cycloaddition of conjugated β-alkynyl ketones **1** under known systems,[5] attempting to convert oxonium species into isochromenes. Surprisingly, we found that unexpected multiple cleavage of the C(sp^3)−H bond of the methyl group was furnished, leading to dual C−heteroatom bond

Scheme 1. Profiles of Metal-Catalyzed Cyclization of Conjugated β-Alkynyl Ketones



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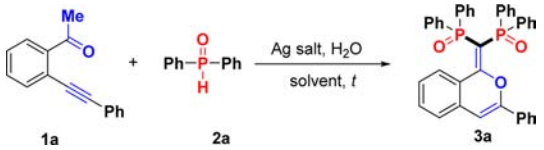
functionalities through radical-enabled cascade process. Herein, we would like to report this discovery of silver-mediated radical C(sp^3)−H biphosphinylation (Scheme 1c). For this reaction, electron-rich diarylphosphine oxide radicals allowed dual C-(sp^3)−H bond functionalization, whereas electron-deficient nitro radicals resulted in a mono C(sp^3)−H bond functionalization due to its deactivating effect on the C═C reactive site. *The present work presents the first radical-triggered double C(sp^3)−H bond phosphinylation of β-alkynyl ketones for the formation of isochromenes through silver-catalyzed 6-endo-dig oxo-cyclization.*

We began our investigations by monitoring the reaction of 1-(2-(phenylethynyl)phenyl)ethanone (**1a**, 0.5 mmol) with diphenylphosphine oxide (**2a**, 1.0 mmol) in the presence of silver salts as both catalyst and oxidant. We first performed the reaction by using AgOAc (1.25 mmol) and H_2O (0.25 mmol) in dry 1,4-dioxane at 120 °C and obtained the corresponding functionalized isochromene **3a**, albeit in a low yield of 29% (Table 1, entry 1). Increasing the dosage of AgOAc (1.5 mmol) facilitated the reaction in a slightly higher yield of 37% (entry 2). However, further increasing the loading of AgOAc to 1.75 mmol decreased the yield of **3a** (entry 3). Screening other silver sources, such as Ag_2CO_3, Ag_2O, and $AgNO_3$, did not show any improvements (entries 4−6). The use of various additional oxidants (1.0 mmol), including 2,3-dichloro-5,6-dicyanobenzo-quinone (DDQ), di-*tert*-butyl peroxide (DTBP), benzoyl peroxide (BPO), $K_2S_2O_8$, and $PhI(OAc)_2$, completely suppressed the reaction process (entries 7−11). We next studied the solvent effect (entries 12−14) by using various solvents such as dry acetonitrile (CH_3CN), 1,2-dichloroethane (DCE), and dimethylformamide (DMF), but less than 31% yield was realized. Then the reaction was performed under an atmosphere of either argon or oxygen, offering poor yields of 12% and 32%, respectively (entries 15 and 16). By taking the combination of 1.5 mmol of AgOAc and 1,4-dioxane as solvent, we varied other parameters of the reaction temperatures and ratios of reactants (entries 17−22). Pleasantly, we found higher temperature (140 °C) and the ratio of 1:1.5 of **1a**/**2a** resulted in a good yield of 74% (entry 20). Without H_2O, the reaction did not proceed, indicating that H_2O plays a key role in the oxo-cyclization process (entry 23).

With the above optimal conditions in hand, we then evaluated the scope of substrates. As shown in Scheme 2, a broad range of

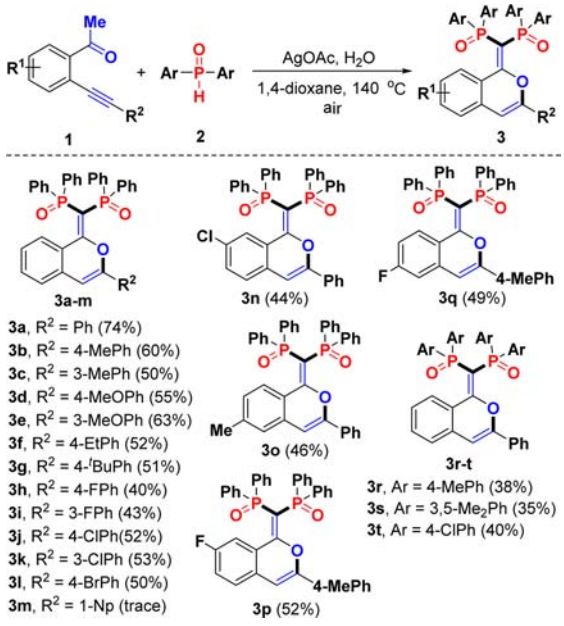
Table 1. Optimization of Reaction Conditions for Product 3a[a]



entry	Ag salts (mmol)	oxidant	solvent	temp (°C)	yield[b] (%)
1	AgOAc (1.25)		1,4-dioxane	120	29
2	AgOAc (1.50)		1,4-dioxane	120	37
3	AgOAc (1.75)		1,4-dioxane	120	31
4	Ag_2CO_3 (0.75)		1,4-dioxane	120	21
5	Ag_2O (0.75)		1,4-dioxane	120	18
6	$AgNO_3$ (1.50)		1,4-dioxane	120	12
7	AgOAc (1.50)	DDQ	1,4-dioxane	120	trace
8	AgOAc (1.50)	DTBP	1,4-dioxane	120	ND
9	AgOAc (1.50)	BPO	1,4-dioxane	120	ND
10	AgOAc (1.50)	$K_2S_2O_8$	1,4-dioxane	120	trace
11	AgOAc (1.50)	$PhI(OAc)_2$	1,4-dioxane	120	trace
12	AgOAc (1.50)		CH_3CN	120	23
13	AgOAc (1.50)		DCE	120	17
14	AgOAc (1.50)		DMF	120	31
15	AgOAc (1.50)		1,4-dioxane	120	12[c]
16	AgOAc (1.50)		1,4-dioxane	120	32[d]
17	AgOAc (1.50)		1,4-dioxane	100	35
18	AgOAc (1.50)		1,4-dioxane	140	43
19	AgOAc (1.50)		1,4-dioxane	150	33
20	AgOAc (1.50)		1,4-dioxane	140	74[e]
21	AgOAc (1.50)		1,4-dioxane	140	47[f]
22	AgOAc (1.50)		1,4-dioxane	140	64[g]
23	AgOAc (1.50)		1,4-dioxane	140	ND[h]

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), Ag salts (*x* mmol) oxidant (1.0 mmol), H_2O (0.25 mmol), and dry solvent (3 mL) in the sealed reaction tube under air conditions for 7.0 h. [b]Isolated yield is based on **2a**. [c]Under Ar conditions. [d]Under O_2 conditions. [e]**2a** (0.75 mmol). [f]**2a** (0.6 mmol). [g]**2a** (0.85 mmol). [h]The reaction system without H_2O. ND = not detected.

Scheme 2. Substrate Scope of Biphosphinylation[a]



[a]Reaction conditions: (i) **1** (0.5 mmol), **2** (0.75 mmol), AgOAc (1.5 mmol), H_2O (0.25 mmol), and dry 1,4-dioxane (3 mL) in a sealed reaction tube under air for 7 h at 140 °C; (*ii*) isolated yield is based on **2**.

conjugated β-alkynyl ketones are applicable to the present 6-*endo-dig* oxo-cyclization and double C(sp^3)−H bond functionalization, in which diphenylphosphine oxide (**2a**) was first subjected to the reaction with these ketones of different electronic properties on their phenyl rings of alkynyl moieties to give the desired isochromene **3b−l** in 40−63% yields. Although the electronic effect on the aryl rings reduced the yields to some extent, the desired products **3b−l** were still generated with yields ranging from 40% to 63%. It seems that the presence of electron-donating substituents (**1b** and **1e**) on the above *p*-phenyl positions favor the reaction more than their electron-withdrawing counterparts (**1h**, **1j**, and **1l**). A sterically encumbered 1-naphthyl (1-Np) analogue (**1m**) only gave a trace amount of **3m**. The substrates **1** with chloro, methyl, and fluoro functionalities at the 4- or 5-positions of acetophenone ring afforded **3n−q** in 44%−52% yields. Regarding the scope of

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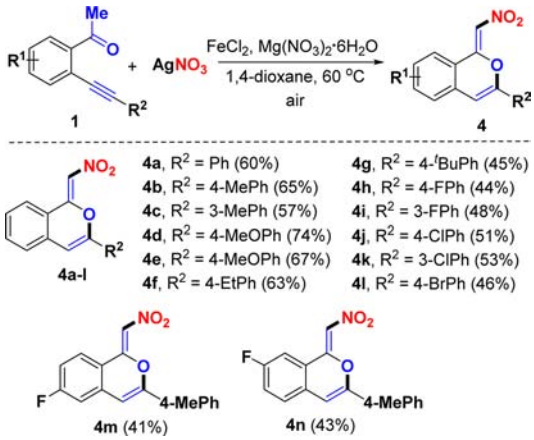
phosphine oxides, besides phenyl (**2a**) substrate, 4-methyl (**2b**), 3,5-dimethyl (**2c**), and 4-chlorophenyl (**2d**) counterparts worked smoothly, enabling direct C(sp^3)−H biphosphinylation to give **3r**−**t** in relatively low yields of 35−40%.

In the meantime, isochromenes containing a nitro-branched motif have captured our attention owing to their potentials in various fields, such as chemistry, medicine, industry, fuels, etc.[9,10] We thus investigated the cyclization/nitration of *β*-alkynyl ketones by using $AgNO_3$ as both a nitrating reagent and catalyst.[11] To our delight, the reaction can be performed in the presence of $AgNO_3$ in 1,4-dioxane at 60 °C under air conditions; in addition, 50 mol % of $FeCl_2$ and $Mg(NO_3)_2{\cdot}6H_2O$ were employed as an additives (see the Supporting Information). A series of nitro-branched (*Z*)-isochromenes **4** were afforded in the range of 41%−74% yields (Scheme 3). It should be noted that

Scheme 3. Substrate Scope of Nitration[a]



[a]Reaction conditions: (i) **1** (0.5 mmol), $AgNO_3$ (0.6 mmol), $FeCl_2$ (0.25 mmol), $Mg(NO_3)_2{\cdot}6H_2O$ (0.25 mmol), and dry 1,4-dioxane (3 mL) in a sealed reaction tube under air conditions for 6 h at 60 °C. (ii) Isolated yield is based on **1**.

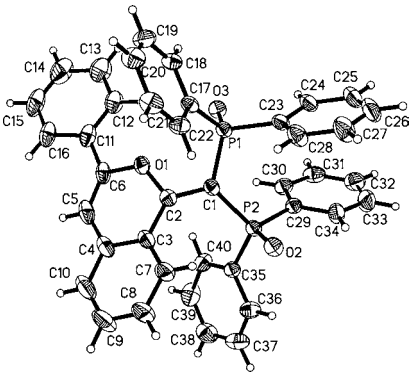
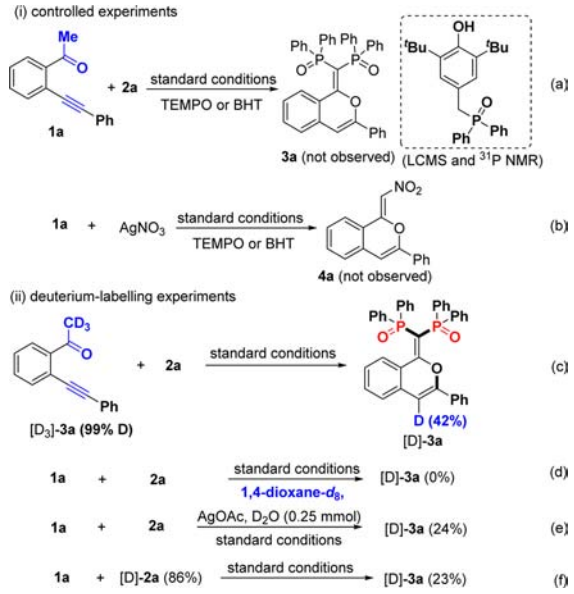


Figure 1. ORTEP Drawing of **3a**.

Scheme 4. Control Experiments



only mono C(sp^3)−H nitration product was observed, which would be attributed to the strong electron-withdrawing effect by the nitro group in deactivating C═C bonds. Similar to the above biphosphinylation version, a series of substituents including Me, MeO, Et, *t*-Bu, F, Cl, etc. at different positions on the arylalkynyl moiety can be engaged in the present system. The fluoro substituent at the 4 or 5 position of the *β*-alkynyl ketone skeleton was also proven to be effective, delivering the corresponding (*Z*)-products **4m** and **4n** in 41% and 43% yields, respectively. Most functionalities of the resulting nitrated products provide great flexibility for structural modifications via reduction reactions. The structures of products **3** and **4** have been fully characterized by NMR and HRMS spectroscopic analysis, and two cases of **3a** (Figure 1) and **4b** were unambiguously confirmed by X-ray diffraction analysis (see the Supporting Information).[12]

To understand the mechanism of this reaction, substrate **1a** was subjected to treatment with **2a** in the presence of AgOAc, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), or butylhydroxytoluene (BHT) (Scheme 4a,b), but no expected product **3a** or **4a** was observed. Among them, a BHT-P adduct was detected by LC−MS and ^{31}P NMR analysis,[13] indicating a radical mechanism under this system. The latter nitration is also believed to proceed through this similar radical process. The deuterium-labeling experiments based on the use of **1a** and **2a** indicated that a hydrogen atom on the new forming pyran ring is generated from diphenylphosphine oxide, H_2O, and the methyl group of *β*-alkynyl ketones (Scheme 4c−f). In Scheme 4c, a kinetic isotope effect (KIE, KIE = 1.38) in a competing reaction of [D_3]-**1a** showed that the C−H bond formation is not rate-limiting step.

On the basis of the above observations and previous information in literature survey,[5] reasonable mechanisms for forming isochromenes **3** and **4** are given in Scheme 5. First, silver salt mediated diphenylphosphine oxide generates the P-centered radical through single-electron transfer (SET, Scheme 5a),[14] whereas iron(II)-mediated decomposition of nitrate anion releases the nitro radical under heating conditions (Scheme 5b). Second, Ag-catalyzed 6-*endo-dig* oxo-cyclzation of *β*-alkynyl ketones in the presence of H_2O generates intermediate **C** through continuous H-transfer (**A** to **C**). Then, the intermolecular addition of R-radical onto alkenyl unit of isochromene **C** yields radical intermediate **D**, followed SET oxidation and deprotonation to *Z*-products **4** (R = NO_2, route i) or *Z*-intermediate **F** (route ii) owing to steric hindrance. Since tge Ph_2PO group is electron rich, it can activate the C═C bond attached by itself.[15] Another intermolecular addition of P-centered radical onto alkenyl unit of **F** occurs, which undergoes SET oxidation and deprotonation to afford the final isochromene products **3**.

In summary, we have established a novel catalytic dual C(sp^3)−H functionalization and cyclization of conjugated *β*-alkynyl ketones, providing an access to a wide range of richly

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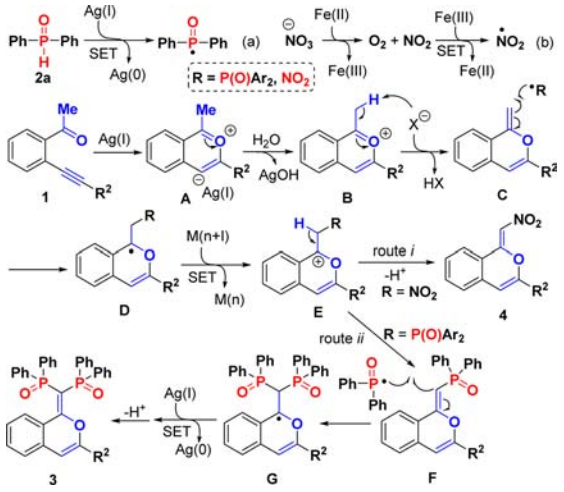
Scheme 5. Plausible Reaction Pathway



decorated isochromenes. The reaction can be selectively controlled toward formation of either dual phosphinyl or mono-nitro-anchored isochromenes by using different radical sources. The mechanism was proposed to involve a sequential Ag-catalyzed 6-*endo*-*dig* oxo-cycilzation/H-transfer/SET/radical addition steps. Further investigation on understanding the reaction mechanism and its applications will be conducted in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03546.

Experimental procedures and spectroscopic data for all new compounds **3a**–**t** and **4a**–**n** (PDF)
X-ray data for **3a** (CIF)
X-ray data for **4b** (CIF)

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‖J.S. and J.-K.Q. contributed equally.

Notes

The authors declare no competing financial interest.

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